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Apparently New Syndrome of Congenital Cataracts, Sensorineural Deafness, Down Syndrome-like Facial Appearance, Short Stature, and Mental Retardation

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We describe a previously unrecognized syndrome in two unrelated patients with congenital cataracts, sensorineural deafness, distinctive facial appearance, skeletal changes, postnatal short stature, and mental retardation. © 1996 Wiley-Liss, Inc.

KEY WORDS: **MCA-MR syndrome, cataracts, sensorineural deafness, short stature, Down-like facial appearance, skeletal abnormalities**

INTRODUCTION

Recently we saw two unrelated patients with an apparently unique combination of bilateral congenital cataracts, sensorineural deafness and distinctive facial appearance, mental retardation with autistic manifestations, postnatal short stature, and skeletal changes.

CLINICAL REPORTS

Patient 1

D.F. is the daughter of healthy, nonconsanguineous parents and has a healthy brother and a healthy maternal half brother. During the fourth month of pregnancy her mother noted fetal movements described as "quivering," very different from those noted in her previous pregnancy. After an otherwise uncomplicated pregnancy D.F. was born vaginally at 35 weeks gestational age to a 26-year-old mother and a 30-year-old father. Birth weight was 2150 g, length 46 cm. Apgar scores were 8 and 9 at 1 and 5 min, respectively. Shortness and bowing of forearms due to radioulnar synostosis and Down-like appearance (Figs. 1 and 2) were noted. High resolution karyotyping showed a 46,XX pattern with no obvious abnormality. No evidence of congenital infection and metabolic diseases was found.

Bilateral dense cataracts were removed at 4 months. The anterior fontanel was unusually wide (8 × 5.5 cm at 4 months) and stayed open until age 3 years. At 18 months an idiopathic left pleural effusion occurred. Idiopathic pericardial effusions developed at 19 and 20 months, each requiring placement of a pericardial window. A left diaphragmatic Morgagni hernia was repaired at 29 months.

D.F. had multiple episodes of acute otitis media requiring middle ear ventilatory tube placement. Brainstem acoustic evoked potentials at 33 months showed responses suggestive of "an underdeveloped nervous system." At 6 9/12 years she was diagnosed as having bilateral mixed hearing loss and received hearing aids.

D.F. was developmentally delayed; at 6 11/12 years developmental assessment indicated a functioning level of about half her chronologic age. Febrile seizures occurred and at 4 years absence spells were recognized and treated with Tegretol® and later with Valproate® and Tranxene®. A brain MRI scan showed a Chiari I malformation and a J-shaped sella turcica.

Physical exam at 9 9/12 years documented height of 125 cm (50% for 8 years), span 119.6 cm, weight 25.6 kg (10–25%), OFC 49.4 cm (2 SD below mean). There was hypertelorism with an inner canthal distance of 3.7 cm (>97%) and an outer canthal distance of 8.2 cm (25–50%). The nasal bridge was broad and low, the nose short with a broad flare at the alae nasi as well as a blunt tip (Figs. 3, 4, and 5). The mouth appeared small with a thin upper lip and a broad and smooth philtrum. Cardiac examination revealed no thrills, no clicks, and no murmurs. Neurologic examination did not show any focal abnormalities.

Koilonychia was present. The skeletal habitus was of normal proportions in the lower limbs, but mild mesomelic shortness in the upper limbs was associated with lateral bowing of both forearms. The elbows lacked about 45 degrees of extension and pronation, there was a 5% hip flexion contracture, and the knees lacked 15 degrees of extension.

Patient 2

J.N. is the son of healthy, nonconsanguineous parents who have 2 older healthy children. After an un-

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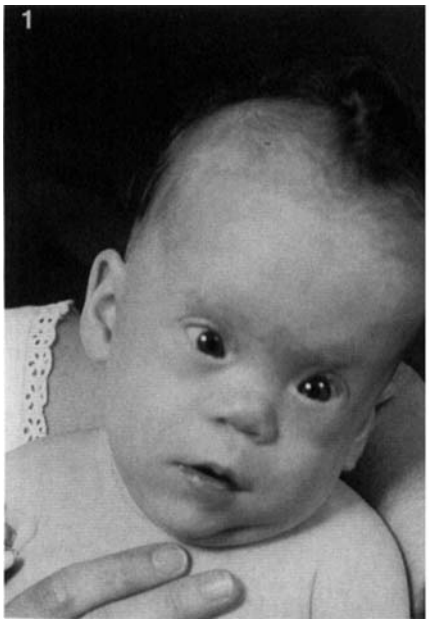

Fig. 1. Patient 1 at age 4 months. Note upslant of palpebral fissures, short nose, long and flat philtrum, small mouth with thin upper lip, and inverted V-shape.

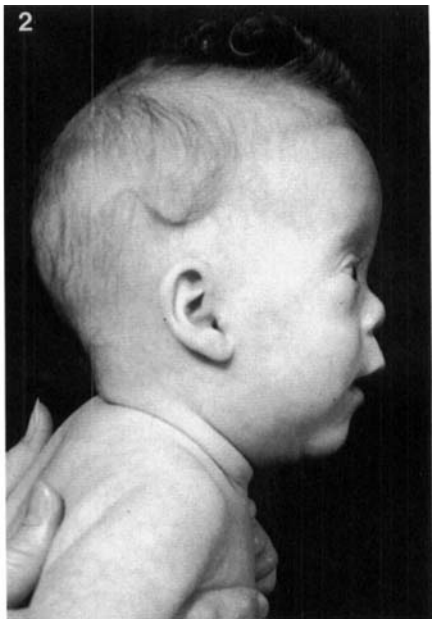

Fig. 2. Patient 1 at age 4 months. Flat face with short nose and long philtrum, ears not angulated or low-set.

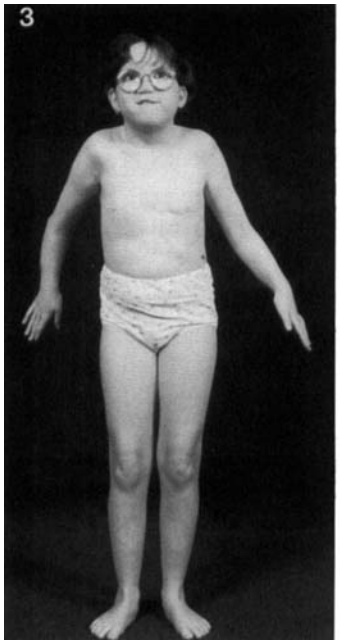

Fig. 3. Patient 1 at 9 years. Broad flare of the alae nasi, small mouth with thin lips, broad and smooth philtrum, flexion contractures of elbows.

Fig. 4. Patient 1 at 9 years, wearing spectacles and hearing aid. Note flat face, mesomelic shortness of upper limbs, flexion contractures of elbows, hips, and knees.

Fig. 5. Patient 1 at 9 years. Showing flat face, short nose with blunt tip, long philtrum, and hearing aid.

complicated pregnancy J.N. was born vaginally at 42 weeks gestational age to a 27-year-old mother and a 30-year-old father. Birth weight was 3960 g, length was 52 cm. Apgar scores were 9 and 9 at 1 and 5 min, respectively. A 2 vessel cord was noted. Congenital right testicular torsion required surgery during the neonatal period; at 7 months a left inguinal hernia with hydrocele was repaired. Bilateral dense zonular central cataracts were removed at 5 and 7 months; the eyes were otherwise normal.

J.N. had multiple episodes of acute otitis media requiring tube placement. He was also diagnosed with bi-

lateral sensorineural hearing loss and received hearing aids at 17 months.

As an infant J.N. did not like to be held or cuddled and at 27 months his developmental age was less than half his chronological age. At 8 months a CT scan of his CNS showed mild ventricular dilatation; an EEG was normal. At 4 years he was found to have autistic manifestations and the diagnosis of "atypical pervasive development disorder" was made.

J.N. frequently gazes at spinning objects and has achieved an amazing ability to spin all kinds of objects on his fingertips. At 14 years J.N. started to limp. X-Ray studies demonstrated narrowness of the joint space in the left hip and idiopathic chondrolysis. Worsening of this process led to total hip replacement at 16 years and a histopathologic study supported the diagnosis of idiopathic chondrolysis.

Physical exam at 15½ years showed a mentally retarded, nonverbal white adolescent male, Tanner stage IV–V. Height was 153.2 cm (50% for 13$^{7}/_{12}$ years); span 150 cm; weight 48.8 kg (50% for 14 years 0 month); OFC 54.3 cm (within 2 SD).

He had upslanted palpebral fissures, a short nose with a nondepressed bridge, inverted V-shaped small mouth, a slightly prominent chin (Fig. 6), very low nuchal hairline, and a broad neck with mild pterygium. Cardiac examination revealed no thrills, no clicks, and no murmurs. Neurologic examination did not show any focal abnormalities. Bilateral brachyclinodactyly V (palm right 9.7 and left 9.4 cm; 3rd finger 7.4 and 7.6 cm; all within normal limits), slight prominence of the proximal interphalangeal joints of all fingers, and inability to bear weight on the left hip were noted.

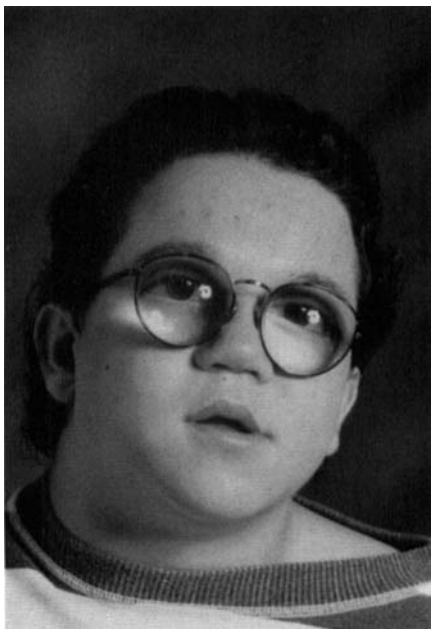

Fig. 6. Patient 2 at age 16 years; note similarity to Patient 1. Short nose with broad flare of the alae nasi, long and smooth philtrum, small inverted V-shaped mouth.

Results of studies for congenital infection and inborn errors of metabolism were within normal limits; a high resolution karyotype was 46,XY. Specifically probe studies for the Smith–Magenis syndrome and Xp22.3 did not show any microdeletion.

DISCUSSION

The 2 above-described patients share findings of congenital cataracts, early-onset sensorineural hearing loss, mental retardation, short stature, and unusual face with short nose and small mouth. Both patients show skeletal changes, patient 1 having bilateral radioulnar synostosis with shortness and bowing of the forearms, a J-shaped sella, and late closure of the fontanel; patient 2 developed idiopathic chondrolysis (Table I). A number of clinicians had commented about possible Down syndrome, however cytogenetic studies excluded this.

Cataracts and hearing loss represent characteristic findings in several hereditary disorders [McKusick, 1994], but our patients lack other manifestations of such syndromes, e.g., the nephropathy of Alport syndrome, loss of adipose tissue in infancy in the Cockayne syndrome, the marfanoid habitus seen in some cases of the Stickler syndrome, partial albinism of Waardenburg syndrome, and typical face of Marshall syndrome, and so forth.

Nadol and Burgess [1982] and Guala et al. [1992] described an autosomal dominant syndrome of sensorineural deafness and cataracts. In these patients the hearing loss had an onset in the mid-twenties and no mental retardation or short stature was noted, therefore our patients do not match this description.

A boy seen by Bader et al. [1985] had a number of findings in common with our patients, such as cataract, sensorineural deafness, short stature, and skeletal changes; however, he and his mother had brachydactyly with cone-shaped epiphyses. Our patient 2 had brachydactyly V bilaterally, but the other fingers were not brachydactylic by measurement and there were no cone-shaped epiphyses.

Nucci and Mets [1990] found congenital cataracts, hearing loss, and possible mental retardation in 2 brothers; unlike our cases, these patients also had hypercholesterolemia and congenital spasticity of the legs but no short stature was noted.

Begeer et al. [1991] described 2 sisters with mental retardation, congenital cataract, sensorineural deafness, ataxia, and polyneuropathy. However, the sensorineural deafness and the other neurologic changes became evident only in the third decade of life. Suthers et al. [1993] saw a boy who had deafness, bilateral cataracts, developmental delay, and brachycephaly with increased intracranial pressure but without synostosis. He differs from our patients on the basis of his flat face with depressed nasal bridge, apparently low-set posteriorly angulated ears, and thin upper lip as well as in other findings.

The so called "Binder syndrome" [maxillonasal dysplasia] is not regarded by Gorlin as a true syndrome [Gorlin et al., 1990, p. 813]. This "syndrome" was not considered as our patients did not have absent frontal sinuses or mandibular prognathism. Likewise, we do

TABLE I. Summary of Clinical Findings

	Patient 1	Patient 2
Mental retardation	+	+, with autistic features
Seizure disorder	Febrile, absence	−
Short stature	<5%	<5%
Bilateral congenital cataracts	+	+
Bilateral sensorineural deafness	+	+
Short nose	+	+
Small mouth	+	+
Low hairline	−	+
Skeletal abnormalities	Bilateral radioulnar synostosis; late fontanel closure; J-shaped sella	Idiopathic chondrolysis
Other	Diaphragmatic Morgagni hernia; pericardial effusion	Inguinal hernia; hydrocele

not think that there is evidence of pseudohypoparathyroidism and there was no use of warfarin or other anticoagulants. Chondrodysplasia punctata was ruled out since radiographs at birth of patient 1 do not show stippling of the epiphyses.

Curry et al. [1984] and Ballabio et al. [1991] described male patients with short stature, chondrodysplasia punctata, nasal hypoplasia, ichthyosis, and mental retardation caused by a deletion of Xp22.3, including the steroid sulfatase gene. Chromosome study, and in patient 2 also a molecular study using the probe for the steroid sulfatase gene, failed to show a deletion in our patients; further, they have neither chondrodysplasia punctata nor ichthyosis.

Langer mesomelic dysplasia [Langer, 1967] and its heterozygous state, Léri–Weill dyschondrosteosis [Langer, 1965], show neither deafness nor cataracts.

Radioulnar synostosis can occur with multiple syndromes, only a few of which also are associated with sensorineural or mixed deafness. However, our patients lack characteristics of these syndromes, e.g., the Treacher–Collins like face of Nager and Miller syndrome, the cleft palate and coloboma of Abbruzo–Erickson syndrome, and the tear duct stenosis of Levy–Hollister syndrome. Pallister–Killian syndrome was ruled out by fibroblast karyotypes. Further, none of these conditions shows congenital cataracts or a Down-like face [Stevenson et al., 1993]. A review of the P.O.S.S.U.M. and the London Dysmorphology Database did not show a syndrome in which cataracts, deafness, Down-like face, and skeletal abnormalities occur. Consultation with other clinical geneticists failed to identify a recognizable syndrome.

A history of environmental teratogen exposure was not obtained in either patient. Fetal rubella syndrome can present with mental retardation, cataracts, deafness, and growth deficiency, but is not associated with radioulnar synostosis. Tests for prenatal infections were nondiagnostic in both patients, as were screening metabolic studies of amino acids in serum, organic acids in urine, and screening urinary tests. Due to suspected peroxisomal disorder in case 1 very long chain fatty acids and phytanic acid levels were measured and found to be normal. Repeated high resolution karyotypes from lymphocytes and fibroblasts in both patients did not show any abnormality.

After excluding the more common causes of some of the abnormalities in our patients we conclude that these 2 unrelated patients have a previously unreported syndrome consisting of congenital cataracts, sensorineural deafness, Down-like face, mental retardation, short stature, and skeletal changes.

Because this syndrome occurred in a male and in a female patient with unaffected parents, autosomal recessive inheritance is postulated, although a new dominant mutation or other causes have not been ruled out. Until more cases have been reported the cause remains unknown and recurrence risk cannot be established with certainty.

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